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Research Article

A COMPARATIVE STUDY OF CAUDAL BUTORPHANOL AND FENTANYL FOR ALLEVIATING POST-OPERATIVE PAIN IN INFRAUMBILICAL PROCEDURES IN CHILDREN BELOW 3 YEARS OF AGE

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ABSTRACT

Objective: Caudal block is a common regional anesthetic technique used in children. However, it is limited by relatively shorter duration of analgesia. The objective of this study was to compare the analgesic efficacy of caudal blockade using butorphanol (1) and fentanyl in children below 3 years, undergoing infraumbilical surgeries.

Methods: Patients were randomly allocated to two groups of 30 each. Without premedication, patients were induced with thiopentone, relaxed with atracurium for facilitation of LMA insertion, and maintained on O_2, N_2O, and halothane. Caudal block was then performed using an aseptic technique. One group received caudal butorphanol (25 µg/kg) with 0.25% bupivacaine (0.1 ml/kg) and the other received fentanyl (1 µg/kg). Incision was allowed after 15 min of block. After the completion of surgery, LMA was removed and patients were shifted to the PACU. Non-invasive blood pressure and heart rate were recorded; pain was assessed using modified objective pain score (MOPS) (2) at 2, 4, 6, 12, and 24 h, postoperatively. Oral paracetamol was given at a score >4.

Results: The mean duration of analgesia in Group F was 12.47 (standard deviation [SD] 8.216) and 19.67 (SD 7.009) in Group B (p: 0.001, HS). Mean MOPS was 4.6 in the fentanyl group as compared to 2.6 in the butorphanol group at the end of 24 h (p=0.001, HS). Thus, butorphanol provided longer duration of analgesia compared to fentanyl.

Conclusion: Caudal additives are safe in children and butorphanol provides significantly longer duration of analgesia as compared to fentanyl, thus avoiding caudal catheterization and intravenous analgesics.

Key words: Post-operative analgesia, Modified objective pain score, Caudal block, Caudal additives, Pediatric analgesia.

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INTRODUCTION

In the past decades, there has been a substantial progress in the understanding of infants' and children's sensation and responses to pain [1]. Pain is a challenging and poorly understood speciality as determining accurate objectives, and assessment of pain is difficult, especially in younger age group, who have long been under-medicated for acute pain. Physical pain in children was found to affect emergence from general anesthesia [2] as well as psychologically, in their adulthood.

Regional anesthetic techniques are now an integral part of perioperative and procedure-related pain management in children [3]. Caudal block is a common regional anesthetic technique, generally considered a simple and safe procedure and provides excellent analgesia during surgery as well as in the post-operative period in children. It has been found to reduce the perioperative stress response, requirement of inhalational agent, and perioperative intravenous narcotic use [4,5]. The analgesia is of superior quality with a duration of action lasting for about 4–8 h [6].

A major breakthrough in prolonging the post-operative analgesia in children was the administration of adjuvants along with local anesthetics. Initially, epinephrine with a concentration of 1:200,000 was tried for years [7]. Clonidine and ketamine as caudal adjuvants are currently used but carry the risk of bradycardia, hypotension, and post-operative delirium in children [8]. Opioids as caudal adjuvants, although debatable, are a well-known practice in children. Several drugs including morphine, fentanyl, buprenorphine, and tramadol along with anxiolytics like midazolam and alpha-agonists such as dexmedetomidine and clonidine are currently used as adjuvants along with local anesthetics for caudal block in children. Caudal butorphanol has also been studied in adults where it showed a longer lasting (7.46±1.35 h) analgesia with minimal side effects [9].

In the current study, we used butorphanol which is a synthetic opioid analgesic with agonist-antagonist activities at mu and kappa receptors, found to be relatively safe with fewer side effects in children. We conducted prospective, randomized, double-blind trial to compare the effects of caudal butorphanol and fentanyl with isobaric bupivacaine (0.25%) with respect to alleviation of post-operative pain in children undergoing infraumbilical surgeries.

METHODS

After availing the approval from the Institutional Ethical Committee (Annexure 1), this study was conducted in the hospitals associated with Kasturba Medical College, Mangalore, from the year 2013 to July 2015. The study participants included 60 children aged between 6 months and 3 years undergoing infraumbilical surgeries.

Design

The study was a double-blind, prospective, randomized, clinical trial.

Aim and objective

This study aims to compare the analgesic efficacy of caudal blockade using butorphanol and fentanyl in children below 3 years undergoing infraumbilical surgeries.

Inclusion criteria

Participants of age group 6 months–3 years, of either sex, of the American Society of Anesthesiologists (ASA) physical status 1 and 2 undergoing infraumbilical surgeries were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

1. Parent/guardian refusal
2. ASA physical status 3 and 4
3. Children weighing more than 15 kg and <5 kg.
4. Participants with a history of allergy to any of the study drugs
5. Hemodynamically unstable patient including coagulation abnormalities
6. Acute emergencies
7. Sacral anomalies
8. Systemic diseases including seizure disorders.

Sample size

The sample size required for correctly rejecting the null hypothesis with the power of 80% and confidence interval of 95% was calculated and was determined that 60 participants were required with 30 participants in each group.

The sample size was calculated using the formula [10]

$$n = \frac{2(Z_\alpha + Z_\beta)^2 \times \sigma^2}{d^2}$$

Where,

Z_α = 95% confidence interval

Z_β = 80% power

σ = Standard deviation

d = mean difference

Method

The selected patients were randomly allocated using computer-generated list of random numbers into two groups of 30 each. Ethics committee approval was obtained from Manipal University and an informed written parental consent was obtained. Pre-operative evaluation was done to all the patients. No premedication was given to any patient in either group. All patients were prior cannulated for the administration of antibiotics or drawing samples for blood investigations before shifting to the operating theater. In the operation theater, the nil-per-oral status was confirmed; standard ASA monitors were connected, intravenous line patency reconfirmed and maintenance fluid: Lactated Ringer's solution was started. Patients were induced with regular doses of thiopentone sodium (5–7 mg/kg) and neuromuscular blockade achieved with atracurium (0.5 mg/kg) to facilitate LMA insertion and were maintained on oxygen with FiO_2 of 0.5 and nitrous oxide, with halothane as inhalational agent. No intravenous or per rectal analgesic drugs of any genre were administered to any patient intraoperatively. All patients in both the groups were connected to the anesthesia ventilators on volume-controlled ventilation mode using appropriate tidal volume and respiratory rate corresponding to weight.

In the two groups, Group B received caudal butorphanol at a dose of 25 µg/kg with 0.25% isobaric bupivacaine and Group F received fentanyl at a dose of 1 µg/kg with 0.25% isobaric bupivacaine. The dose of bupivacaine was calculated at 1 ml/kg without adding vasoconstrictors and keeping the toxic dose into consideration. Hemodynamic parameters such as heart rate, non-invasive blood pressure (NIBP), and end-tidal carbon dioxide were monitored in all patients.

After the induction of anesthesia, patients were placed in the lateral position. Caudal block was performed using an aseptic technique eliciting a pop with a 22 SWG needle. Immediately after the caudal block, the patients were turned supine for the performance of surgical procedure. Skin incision was allowed after 15 min of caudal block and blood pressure with heart rate was recorded just before and after surgical incision and then every 10 min till the end of surgery. If any patient responded to the incision with an increase in blood pressure (>20 mmHg) or heart rate (>20 beats/min), it was considered as failure of caudal block. These patients were excluded from the study and rescue intraoperative analgesia with opioids was provided to them. Toward the end of surgery, injection ondansetron 0.15 mg/kg was given to all patients. After completion of surgery, neuromuscular blockade was reversed with appropriate doses of neostigmine and atropine. LMA was removed when the patient was awake and sent to recovery room and then to the post-operative ward for observation.

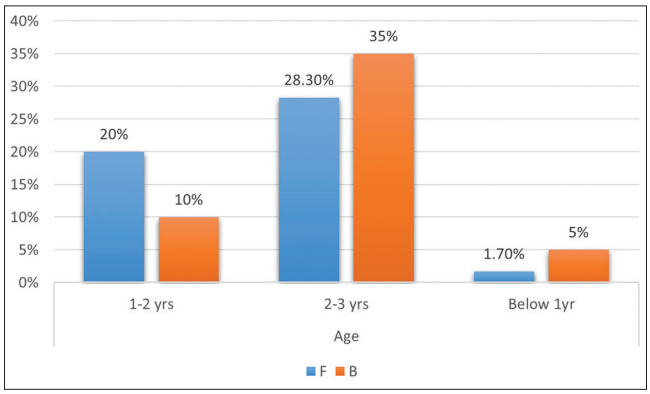
In the recovery room and post-operative ward, when the child was awake, the investigator, unaware of the method of analgesia chosen, recorded the NIBP and heart rate, and assessed the pain at 2, 4, 6, 12, and 24 h, postoperatively. Post-operative pain was assessed using "modified objective pain score (MOPS)" [11]. Rescue analgesia in the form of oral paracetamol (20 mg/kg) was given at a score >4. Side effects/complications were also noted and recorded (Table A).

OBSERVATIONS AND RESULTS

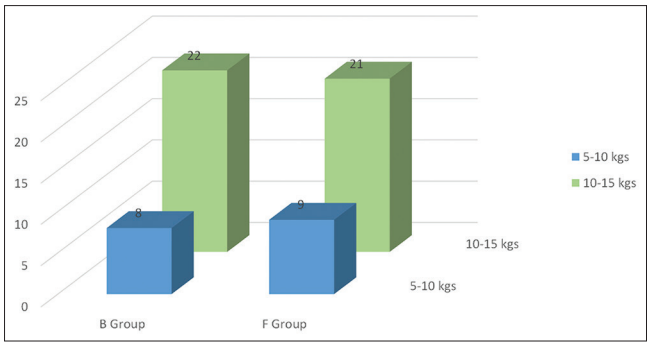
Demographic data of both the groups were compared. Table 1 shows that there was no significant statistically difference. Thus, the two groups were comparable in terms of age and weight (Tables 1a and b, 2 and Graphs 1-4).

The mean duration of analgesia in Group F was 12.47 with a standard deviation of 8.216, and in Group B, mean was 19.67 with a standard deviation of 7.009. The longest duration of action in Group F was 12 h (MOPS 2) and the shortest duration was 2 h (MOPS 5) in Group F. In contrast, the longest duration of action was 24 h (MOPS 0) and the shortest was 6 h (MOPS 6) in Group B (Tables 3-6).

The minimum MOPS in the first 2 h remained 0 in both the groups but reached a maximum of 5 in fentanyl Group (F) and 3 in the butorphanol group (B). In the next 2 h, minimum MOPS remained at 0 in both the groups but reached a maximum of 4 in fentanyl Group (F) and 3 in the butorphanol Group (B). At 6 h, minimum MOPS was 1 in fentanyl (F) group and 0 in the butorphanol (B) group and a maximum of 6 in the fentanyl (F) group and 4 in the butorphanol (B) group. At 12 h, the MOPS



Graph 1: Age distribution



Graph 2: Weight distribution

Table a: Pain score

MOPS			
Score	**0**	**1**	**2**
Movement	None	Restless	Thrashing
Agitation	Asleep/calm	Mild	Hysterical
Posture	Normal	Flexed	Holds injury site
Verbal	Asleep/no complaint	Complains but cannot localize	Complains and localizes

Table 1a: Age distribution

Age	Group		Total
	F	B	
1–2 years	12 (20)	6 (10.0)	18 (30.0)
2–3 years	17 (28.3)	21 (35.0)	38 (63.3)
Below 1 year	1 (1.7)	3 (5.0)	4 (6.7)
Total	30 (50.0)	30 (50.0)	60 (100.0)

χ^2 test; p=0.181, NS

Table 1b: Weight distribution (kg)

Group	N	Mean	SD	*t*-test p value
F	30	12.80	2.932	0.749
B	30	13.07	3.473	NS

SD: Standard deviation

Table 2: Duration of analgesia (hours)

Group	N	Mean	SD	Mann–Whitney U-test p value
F	30	12.47	8.216	0.001
B	30	19.67	7.009	HS

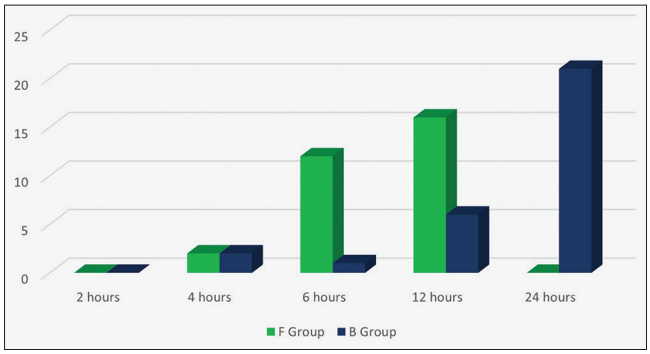
SD: Standard deviation

Table 3: Intraoperative hemodynamic monitoring

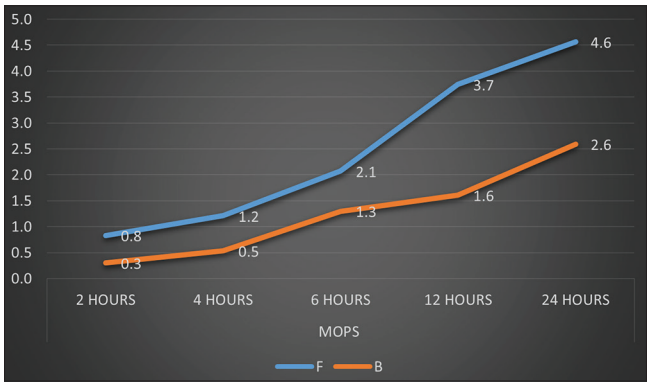
Heart rate (per minute)					
Interval	**Group**	**N**	**Mean**	**SD**	**p value**
Pre-induction	F	30	107.70	16. 382	0.897
	B	30	107.17	15. 407	
Post-induction	F	30	107.33	15. 632	0.390
	B	30	110.47	12. 162	
10 min	F	30	109.50	11. 013	0.872
	B	30	109.97	11. 343	
20 min	F	30	107.57	11. 892	0.833
	B	30	106.93	11. 228	
30 min	F	30	104.00	10. 780	0.922
	B	30	103.73	10. 275	
40 min	F	30	103.00	10.168	0.909
	B	30	102.70	9.994	
50 min	F	30	102.13	9.829	0.857
	B	30	101.67	10.090	
60 min	F	30	101.97	10.284	0.774
	B	30	101.20	10.274	
70 min	F	13	94. 93	9.294	0.087
	B	18	100.63	9.069	
80 min	F	8	96.11	10.410	0.777
	B	11	97.36	9.113	
90 min	F	5	98.00	10.368	0.798
	B	7	96.86	4.488	
100 min	F	1	85.00	N/A	
	B	1	100.00	N/A	

SD: Standard deviation

score remained at minimum of 1 and a maximum of 5 in the fentanyl (F) group and a minimum of 0 and a maximum of 5 in the butorphanol (B) group. Finally, at 24 h, the minimum score remained at a minimum of 5



Graph 3: Duration of analgesia



Graph 4: The duration of analgesia, particularly in the B group, was considerably longer when compared to those done by Vinitha *et al*., in 2006

and a maximum of 6 in the fentanyl (F) group, and at the same time, the minimum score still remained minimum at 0 and maximum of 5 in the butorphanol group.

The above observation shows that the mean MOPS was significantly lesser in the B group for each time measured with p<0.05 at all intervals.

All the patients in both the groups received rescue analgesia when their individual score reached more than 4.

Statistical analysis

Statistical analysis was done with Student's paired *t*-test and χ^2 test. A statistical package SSPS version 15.0 was used to do the analysis. p<0.05 was considered statistically significant.

DISCUSSION

Caudal epidural anesthesia has long gained popularity as a safe regional technique for surgeries in pediatric age group. Commonly a single shot caudal is performed known as "Kiddie caudal" along with general anesthesia for intra- and post-operative analgesia with high success rates [12]. The main disadvantage with single shot technique is the limited duration of analgesia provided with bupivacaine (6.8±2.9 h) [10]. Many drugs have been subsequently experimented in search of the one which prolongs the analgesia with minimal side

Table 4: Systolic blood pressure (mmHg)

Interval	Group	N	Mean	SD	p value
Pre-induction	F	30	97.00	8.670	0.097
	B	30	93.83	5.522	
Post-induction	F	30	93.17	8.558	0.105
	B	30	89.93	6.496	
10 min	F	30	92.63	5.611	0.884
	B	30	92.40	6.673	
20 min	F	30	94.17	6.958	0.535
	B	30	93.17	5.331	
30 min	F	30	94.00	6.074	0.060
	B	30	91.23	5.063	
40 min	F	30	92.83	5.676	0.089
	B	30	90.53	4.577	
50 min	F	30	94.00	6.486	0.181
	B	30	92.00	4.842	
60 min	F	30	94.00	6.486	0.094
	B	30	91.50	4.762	
70 min	F	13	92.31	4.837	0.728
	B	18	91.67	5.145	
80 min	F	8	93.75	5.175	0.658
	B	11	92.73	4.671	
90 min	F	5	94.00	5.477	0.356
	B	7	91.43	3.780	
100 min	F	1	100.00	N/A	N/A
	B	1	90. 00	N/A	

SD: Standard deviation

Table 5: Diastolic blood pressure (mmHg)

Interval	Group	N	Mean	SD	p value
Pre-induction	F	30	60.00	6.017	0.299
	B	30	58.60	4.174	
Post-induction	F	30	57.33	9.072	0.124
	B	30	53.83	8.272	
10 min	F	30	58.60	7.668	0.729
	B	30	58.00	5.509	
20 min	F	30	57.83	6.654	0.913
	B	30	57.67	5.040	
30 min	F	30	58.33	5.774	0.437
	B	30	57.27	4.734	
40 min	F	30	58.17	5.490	0.696
	B	30	57.67	4.302	
50 min	F	30	58.50	4.939	0.343
	B	30	57.33	4.498	
60 min	F	30	58.50	4.939	0.296
	B	30	57.17	4.857	
70 min	F	13	56.54	4.737	0.690
	B	18	57.22	4.609	
80 min	F	8	56.25	5.175	0.373
	B	11	58.18	4.045	
90 min	F	5	58.00	4.472	0.454
	B	7	55.71	5.345	
100 min	F	1	50.00	N/A	N/A
	B	1	60.00	N/A	

SD: Standard deviation

effects including opioids, α agonists, and others. The current study is a simple research in finding out a better and a longer additive to the already widely practiced caudal block.

Fentanyl is a phenylpiperidine-derived synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75–125 times more potent than morphine and synergistically effective with local anesthetics [13]. It is highly lipid soluble and rapidly crosses the blood–brain barrier. It also has a high rate of redistribution, and hence, the level in the plasma and cerebrospinal fluid declines rapidly. It is metabolized by the liver and excreted by the kidneys. Constant *et al*., in 1998, noticed a statistically significant prolonged duration of analgesia in children with lower visual analog score scores in the first 4 h of post-operative period who received bupivacaine with fentanyl than bupivacaine alone but vomiting was the main complication [14]. They observed clonidine to be better substitute than fentanyl in terms of complications. Comparable to this study, Sharmila *et al*. in their comparative study of caudal fentanyl and ketamine noticed a similar duration of analgesia in the first 4 h with fentanyl. They also used serum insulin, cortisol, and glucose as markers for neuroendocrine stress response (NESR), which was not done in any of the previous studies. It was concluded that ketamine 0.5 mg/kg provided a longer duration of analgesia, which was statistically significant; and least NESR was with ketamine which, however, was not statistically significant [15]. Desai further concluded that the children who received 1 μg/kg of fentanyl experienced longer duration of analgesia than patients who received only 0.5 μg/kg of fentanyl [16].

Butorphanol is a morphinan congener having a nitrogen-substituted 3,14-dihydroxymorphine. This synthetic member of the benzomorphan series is structurally similar to other drugs having various degrees of narcotic agonist and antagonist properties at room temperature. Butorphanol exists as white water-soluble crystals. Compared with pentazocine, its agonist effects are about 20 times greater, whereas its antagonist actions are 10–30 times greater. It is speculated that butorphanol has a (a) low affinity for μ receptors to produce antagonism, (b) moderate affinity for κ receptors to produce analgesia and anti-shivering effects, and (c) minimal affinity for σ receptors, so the incidence of dysphoria is low.

Singh *et al*., in 2006, compared the efficacy of caudal butorphanol in three groups of patients who received 1 ml/kg of 0.25% bupivacaine alone (L group). Among the two other groups, Group B received butorphanol 25 μg/kg only in saline and Group LB received 0.25% bupivacaine and 25 μg/kg of butorphanol through caudal route. Mean duration of analgesia was significantly higher in LB group with p=0.001, but the incidence of nausea and vomiting was higher in butorphanol (B) alone and combined group with bupivacaine (LB) but not statistically significant [10].

Similarly, Gupta *et al*., in 2009, made a comparative study in three groups of 0.25% of bupivacaine alone with a combination of the same with 20 μg/kg of butorphanol and 1 mg/kg of tramadol. The duration of analgesia was 435.83 min in the group who received butorphanol

Table 6: Comparison between the groups

MOPS	Group	N	Minimum	Maximum	Mean	SD	Median	Mann–Whitney U-test Z value	p value
2 h	F	30	0	5	0.83	1.117	1	2.74	0.006
	B	30	0	3	0.3	0.702	0		HS
4 h	F	29	0	4	1.21	1.013	1	3.29	0.001
	B	30	0	3	0.53	1.008	0		HS
6 h	F	29	1	6	2.07	1.132	2	3.56	0
	B	30	0	4	1.3	1.291	1		HS
12 h	F	27	1	5	3.74	1.318	4	5.07	0
	B	28	0	5	1.61	0.956	1		HS
24 h	F	16	5	6	4.56	1.094	5	3.4	0.001
	B	27	0	5	2.59	1.623	2		HS

SD: Standard deviation

(statistically significant p value, 0.01), 302.25 min in bupivacaine alone, and surprisingly, 291.08 min in the group who received tramadol with a high incidence of vomiting [17].

In the present prospective randomized double-blind study, we compared the efficacy of caudal fentanyl in a dose of 1 µg/kg and butorphanol 25 µg/kg with 0.25% bupivacaine in 60 patients of two groups F and B, respectively, of 30 each. The sample population were comparable in terms of demographics; age and weight which were statistically insignificant. At induction, intraoperatively and postoperatively, we noticed a stable hemodynamic status in terms of heart rate and systolic and diastolic blood pressure which was not statistically significant (p>0.01).

When comparing the two groups, the MOPS remained at 0 as minimum in the first 4 h in both the groups but remained higher at 5 which required rescue analgesia in the fentanyl group making it statistically significant. No patients in B group required analgesics in any form in the first 4 h. At the end of 6 h, the minimum scores remained at 0 and 1 in butorphanol (B) and fentanyl (F) groups, but the maximum scores still remained at 4 in B group and 6 in the fentanyl group requiring rescue analgesia. At 12 h, the MOPS remained at a minimum of 1 and a maximum of 5 in the fentanyl (F) group and a minimum of 0 and a maximum of 5 in the butorphanol (B) group. Finally, at 24 h, the minimum score remained at 5 and a maximum of 6 in the fentanyl group, and at the same time, the minimum score still remained at 0 and maximum of 5 in butorphanol group.

The mean duration of analgesia was significantly higher in Group B (19.67 h, standard deviation [SD]: 7.009) as compared to Group F (12.47 h, SD 8.216) (p=0.001, highly significant). Minimum MOPS recorded at each hour (2, 4, 6, 12, and 24 h) was <2 for entire 24 h period for both the groups; however, the MOPS recorded at each hour for Group B had significantly lower maximum pain score 3 at 2nd h as compared to Group F 5 with p=0.006 (highly significant), 5 and 6 at 6th h, respectively, with p value of 0 (highly significant), and 6 and 5 at 24th h, respectively, with p=0.001 (highly significant). Mean MOPS was <5 for entire 24 h period for both the groups; however, mean MOPS was significantly lesser in Group B at each recorded hour with p<0.05.

Complications

No complications were noticed in terms of failure of analgesia, post-operative hypoventilation, nausea and vomiting, retention of urine requiring catheterization, itching, or dysphoric reactions in any of the patients in both the groups.

However, there was no long-term follow-up with the patients; hence, long-term side effects cannot be ruled out, which is one of the limitations of this study.

CONCLUSION

1. Adjuvants such as fentanyl 1 µg/kg and butorphanol 25 µg/kg with bupivacaine 0.25% for intra- and post-operative analgesia are safe in children.
2. Reduce the requirement of potent inhalational agents and the need for subsequent analgesics in the post-operative period.
3. Stable hemodynamic status with both fentanyl and butorphanol.
4. Butorphanol offers advantages of the longer duration of analgesia than fentanyl.
5. Avoid caudal catheterization and subsequent catheter-related complications.
6. No complications such as nausea and vomiting. Although post-operative vomiting is a known complication with butorphanol, the incidence is masked due to intraoperative ondansetron.
7. No delayed respiratory depression, itching, dysphoric reaction, and retention of urine. Post-operative motor blockade is not a concern with parents in any of the patients.
8. No neurological sequelae.
9. Decreased parental anxiety and increased satisfaction.
10. Reduced cost factor.

AUTHORS' CONTRIBUTION

Dr. Mohammed Irfanulla: Conceived and designed the analysis, collected and contributed data, performed analysis, and wrote the paper. Dr. TV. Shenoy: Conceived and designed the analysis, performed the analysis, and contributed in writing of paper. Dr. Ranjan RK: Conceived and designed the analysis, and performed analysis.

CONFLICTS OF INTEREST

Nil.

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ANNEXURE 1

प्रज्ञानं ब्रह्म

Manipal
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Kasturba Medical College, Mangalore
A constituent college of Manipal University

Institutional Ethics Committee

Communication of the Decision of the Institutional Ethics Committee

Wednesday 18th December 2013 IEC KMC MLR 12-13/258

Protocol title	:	A Comparative study of Caudal Butorphanol and Fentanyl for alleviating post-operative pain in infraumbilical procedures in children below three years of age
Principal Investigator		Dr. Mohammed Irfanulla
Guide/Co-Guide/Co-Investigators	:	Dr. Thrivikram Shenoy
Name & Address of Institution	:	Department of Anaesthesiology Kasturba Medical College Mangalore
New / review	:	New
Date of review (DD/M/YYYY)		18/12/2013
Decision of the IEC ➢ Approved ➢ Pending ➢ Revision ➢ Rejected	:	Approved from 18/12/2013
Remarks	:	Approved for the study period as mentioned in protocol

Please Note*

- Inform IEC immediately in case any Adverse events and Serious adverse event
- Inform IEC in case of any amendments to the protocol, change of study procedure, site and Investigator and premature termination of study with reasons along with summary.
- Final & Yearly Reports to be submitted to IEC.
- Members of IEC have right to monitor the study with prior intimation.
- A copy of the consent document to be given to the study participant giving the consent.

Dr. Shalini Shenoy
MEMBER SECRETARY-IEC

KASTURBA MEDICAL COLLEGE
INSTITUTIONAL ETHICS COMMITTEE
MANGALORE-575 001

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